Intraoperative magnetic resonance imaging-assisted transsphenoidal pituitary surgery in patients with acromegaly

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Abstract: In this largest study to date of GH-producing pituitary adenomas in which iMR imaging-guided transsphenoidal surgery was analyzed, the results suggest that this method is a highly effective and safe treatment modality, even compared with previously published surgical series in which high-field iMR imaging was used. Limitations of iMR imaging are the detection of small residual tumor in the cavernous sinus and persisting disease that could not be observed, even on diagnostic high-field follow-up MR images. This points to a general limitation regarding remission rates that can be achieved using iMR imaging. Nevertheless, iMR imaging led to an increase of the remission rate in this study.

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Intraoperative magnetic resonance imaging assisted transsphenoidal pituitary surgery in acromegalic patients

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Abstract:

Background: Acromegaly is a rare disease, usually caused by a growth-hormone (GH)-producing pituitary adenoma (PA). If untreated, severe cardiovascular, metabolic, cosmetic and orthopaedic disturbances will result. Surgery is generally recommended as first line treatment. Transsphenoidal surgical techniques were recently extended by introduction of intraoperative magnetic resonance imaging (iMRI).

Objective: In the present study the contribution of ultra-low-field iMRI (0.15 Tesla) for tumor resection, complication avoidance, endocrinological and neurological outcome was analyzed.

Methods: A series of 39 consecutive transsphenoidal iMRI-guided (PoleStar™ N20) surgical procedures performed between September 2005 and August 2009 for GH-producing pituitary adenomas was retrospectively analyzed. Besides patients' clinical data, surgery time, hospital stay, endocrinological parameters, neurological examinations and pre-/post- and intraoperative imaging were evaluated independently.

Results: Thirty-seven patients with acromegaly underwent 39 transsphenoidal surgeries for pituitary adenomas. During median follow-up of 30 months (range 9-56 months) remisson rate was 73.5% in 34 patients with primary surgery and 20.0% in five cases with previous surgery; overall remission rate was 66.7%. There were no serious postoperative complications. Detection of tumor remnant on iMRI led to a 5.1% increase in remisson rate.

Conclusions: In this so far largest study for GH- producing PAs analyzing iMRI-guided transsphenoidal surgery the results suggest that this method is a highly effective and safe treatment modality, even compared to previously published surgical series using high-field iMRI. Limitations of iMRI are the detection of small residuals in the cavernous sinus and persisting disease that could not be referred to even on diagnostic high-field follow-up

MRIs. This points to a general limitation of remission rates that can be achieved by iMRI. Nevertheless iMRI led to an increase of remission rate in this study.

Keywords:

Acromegaly, PoleStar™ N20, intraoperative magnetic resonance tomography, MRI, iMRI, pituitary adenoma, transsphenoidal surgery

Introduction:

Acromegaly is a rare disease with an estimated incidence of about 4 per 10^6 inhabitants. In most cases, it is caused by a growth-hormone (GH)-producing pituitary adenoma (PA). If excessive output of GH is not normalized, severe cardiovascular and metabolic disturbances as well as cosmetic and orthopaedic deformities will result. Previously published studies have shown a 2-3-fold increased mortality for treatment-resistant cases as compared to successfully treated patients and healthy individuals[6,28,36]. Correction of GH values to normal can restore life expectancy towards normal. Most studies and the international consensus conference[9,12,26,27] recommend surgery as first line treatment. Medication with somatostatin analogues can achieve biochemical control in up to 60% of cases but without comparable tumor size reduction. First surgical treatment using a transnasal approach in an acromegalic patient was performed by Dr. Schloffer in Vienna in 1907[31]. Two years later Dr. Cushing did a partial hypophysectomy in a patient with acromegaly assuming that the underlying pathomechanism was a hypertrophy of the pituitary gland[10]. Surgical techniques and non-surgical treatment options have developed ever since[23]. Today, most patients receive surgery as first line treatment using a transnasal, transsphenoidal approach introduced by Cushing and reintroduced using microsurgical techniques by Hardy in 1979[18]. More recently developed refinements in this surgical approach include the introduction of endoscopy[3,8,20,22] for pituitary surgery and iMRI[4,14]. In this so far largest study using ultra-low-field iMRI in GH producing pituitary adenomas, we analyzed retrospectively a series of 39 consecutive cases using a transnasal, transsphenoidal microsurgical iMRI-assisted approach with the PoleStar™ N20 (0.15 Tesla).

Patients and methods

Patient demographics:

Thirty-nine surgical interventions were performed on 37 (24 male) patients suffering from GH-producing pituitary adenomas between September 2005 and August 2009. Two patients (one male) were operated twice. All patients were transsphenoidally operated by the senior author using an ultra-low-field iMRI. Mean age was 47±14 years (median 46, range 19-76 years). The median preoperative tumor size was 1319 mm^3; (mean: 3360mm^3 range: 50-56549mm^3). Ten cases (25.6%) presented with microadenomas, 27 (69.2%) with macroadenomas and 2 (5.1%) with giant adenomas. There were five patients with previous pituitary surgery (12.8%). In 11 cases (28.2%) the tumor invaded the cavernous sinus. In 37 cases (94.8%), patients had symptoms of acromegaly and 8 patients (20.5%) had cranial nerve symptoms, among them five with visual field deficits.

Pre- and postoperative management:

Patients were seen as outpatients before surgery. After decision for surgical treatment, patients arrived in hospital the day before surgery. Preoperative diagnostics included computed tomography (CT) scan and magnetic resonance imaging (MRI) for determination of the pituitary adenoma, bony and neurovascular structures. Pre- and postoperative imaging studies were performed at the Department of Neuroradiology, University Hospital of Zurich. CT studies were performed on a 16 slice CT scanner (Siemens SOMATON® Sensation, München, Germany) acquiring non contrast-enhanced and contrast-enhanced multi slice imaging data. The MRI studies were performed on a 1.5 Tesla MR tomography scanner (Signa®, General Electric, New York City, USA).

Neurological and ophthalmological examinations were performed after admission. General patient data, additional diagnosis, medication at admission and previous study results were noted. Patients underwent endocrinological examination which included blood analysis for pituitary function examining growth hormone (GH), insulin-like growth factor-1

(IGF-1), adenocorticotropin hormone (ACTH), cortisol, thyroid stimulating hormone (TSH), fT4, fT3, prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH) and human chorionic gonadotropin (hCG); testosterone was measured in male and estradiol in female patients unless a history of recent menstrual bleedings or of contraceptive pill intake was given.

Patients signed written consent for the surgical procedure and general anaesthesia. At the day of surgery, most patients received, for safety reasons, 100mg hydrocortisone (SoluCortef®, Pfizer, New York City, USA) one hour before operation, and. another dose of 100mg hydrocortisone was given perioperatively. After surgery, patients were transferred to intermediate care unit (IMCU). A postoperative CT scan was performed in all patients around six hours after surgery to exclude major bleeding or serious complications. The next morning patients were transferred to the general ward and mobilized. They received 100mg of hydrocortisone on the first and 50mg on the second postoperative day. On the morning of the third operative day and/or before discharge, pituitary function was re-examined. If patients' cortisol levels were below 200nmol./l in fasting blood samples, they received 30mg of hydrocortisone (Hydrocortone®, Merck, Darmstadt, Germany) per day until endocrinological follow-up as outpatients four weeks after surgery.

Surgery and intraoperative neuroimaging:

All operations were performed in general anaesthesia. Patients were put in supine position on a foldable standard operation table with their head slightly reclined. The head was then fixed in a MRI-compatible head holder after adjusting the radio frequency coil around the patients head. The iMRI scanner used in all patients was a PoleStar™ N20 (0.15 Tesla, Medtronic Navigation, Louisville, CO, USA). Afterwards the intraoperative navigation system (Stealth Station, Medtronic Navigation, Louisville, CO, USA) was

referenced with preoperative CT studies. The position of the patient's head in the scanner was tested by performing a 24 second sagittal e-steady scan (8mm slices) and adjusted if necessary. Before surgery, a 7-minute, T1-weighted, gadolinium (20 ml Dotarem®, Guerbet, Roissy CdG Cedex, France) enhanced, 4mm slice, coronal iMRI scan was performed. These images were automatically loaded into the navigation system and merged with the preoperative imaging studies.

All parts of surgical procedures were performed by using an operating microscope (Pentero®, Carl Zeiss, Oberkochen, Germany). At the beginning of operations a self-retaining endonasal speculum was inserted in the nostril chosen for surgical approach. The mucosa was incised and partially removed, the posterior bony part of the septum was removed and the anterior wall of the sphenoid sinus was displayed. The anterior wall of the sphenoid sinus was then opened with punches, the intrasphenoidal mucosa and septum were removed and the inferior and anterior surface of the sella was displayed and opened with a chisel. The dura mater was opened in an x-shaped fashion and the adenoma removed by curettes, grasping forceps and suction devices. Tumor material was sent for frozen sections and neurohistopathological examination. After complete tumor removal according to the surgeon's impression, a 3.5-minute, T1-weighted, gadolinium-enhanced, 4mm slice, coronal iMRI scan was performed for resection control in all patients. For better visualisation of possible tumor remnants, a glove-covered ball of bone wax was inserted into the resection cavity for hemostasis and improved interpretation of intraoperative images. The intraoperatively acquired images were automatically merged with the existing preoperative and intraoperative imaging studies. In cases of visible tumor remnant, the resection cavity was re-examined and tumor remnants removed if possible. Another post-resectional, intraoperative 3.5-minute, T1-weighted, gadolinium- enhanced, 4mm slice, coronal iMRI scan was performed in those cases. The anterior wall of the sella turcica was reconstructed by using the extracted posterior part of the bony nasal or

intrasphenoidal septum. In cases of intraoperative CSF leakage, the sella was packed with abdominal fat and use of fibrin sealant. No nasal packing was used. All operations were performed by the senior author.

Follow-up:

All patients were followed-up four weeks postoperatively as outpatients in the endocrinology clinic; hormone levels were analyzed and deficiencies replaced if necessary. Three months after surgery, patients received a postoperative MRI study for resection control and patients were seen for neurosurgical follow up and examination. Patients were only defined as being in remission if symptoms of acromegaly disappeared, IGF-1 levels returned into the age-adjusted reference range and GH levels decreased to <1.0ug/l. In case of clinical improvement, normalization of IGF-1 level and GH level between 1.0ug/l and 5.0ug/l, a glucose tolerance test was performed. Patients suppressing GH to <1.0ug/l in the glucose tolerance test were defined as being in remission as well.

Statistical analysis and neuroimaging:

The statistical analysis was performed using Microsoft Excel (Version 2003) and SPSS Statistic software (Version 16.0). All imaging studies were analyzed independently and blinded to the clinical outcome using standardized software (picture archiving and communication system, PACS). Tumor volume was calculated based on the diameter method (Tumor volume = 4/3 * Pi * ½x * ½y * ½z), where x, y and z are the maximum diameters in the three axis.

Results:

Intraoperative imaging studies:

Intraoperatively, 2.2±0.53 (median 2; range 1-4) imaging studies were performed per case. There was one iMRI imaging at the beginning of surgery in all cases. In all cases a second iMRI imaging was performed before closing (illustrative case see Figure 02). In eight cases (20.5%) the second iMRI revealed a tumor remnant and further tumor removal was performed. In most of those cases (7 out of 8 cases) a third imaging study was done. In one case, a the third iMRI revealed tumor remnant even after further tumor removal that could not be safely resected and therefore was left in place. Out of the 8 patients with additional tumor removal after second iMRI, 7 patients were considered tumor remnant-free after the second intraoperative imaging study. Five out of those seven patients (71.4%) showed tumor remnant on three months diagnostic follow-up high field MRI studies. The median tumor remnant size in these patients was 4mm^3 (range 4-147). In comparison, only two out of 31 patients (6.4%) that were considered tumor remnant-free after first intraoperative imaging study showed tumor remnant at three months follow up. There were two patients (5.1%) in whichresidual tumor was found on iMRI, subsequently resected and leading to endocrinological remission.

Duration of surgical procedures:

Median duration of the surgical procedure including iMRI scanning time was 90 minutes (mean 91.7, range 30-235 minutes). Table 5 shows that median duration of operations in patients with previous surgery (105 minutes; range: 60-235 minutes) was longer than in patients with first time surgery (median 88 minutes; range: 30-180 minutes). Median duration of operations in patients with infiltration of cavernous sinus (118 minutes; range: 55-235 minutes) was prolonged versus patients without infiltration (median 72.5 minutes; range: 30-170 minutes). Aquiring of iMRI was responsible for interruption of the surgical procedure for between 5 and 10 minutes depending on the different sequences. In

average this added up to around 25 minutes including one eSteady and 3 T1-weighted contrast enhanced imaging studies.

Postoperative course and complications:

Patients' median time of hospitalization was 7 (range 5-17) days. The immuno-histological examination revealed variable GH positive adenoma tissue in all cases.

Postoperatively, one patient developed signs of CSF rhinorrhea and needed lumbar drainage for five days. Another patient developed diabetes insipidus and needed temporary treatment with desmopressin. There was no case of major postoperative haemorrhage or other complications with need for reoperation.

Endocrinological outcome (Table 02):

All patients were seen for endocrinological follow up four weeks after surgery and surgical follow up after 12 weeks in the hospital's outpatient department. At follow up, there were 30 cases (76.9%) with normalization of preoperative GH and IGF-1 excess. Applying the definition of remission according to the international consensus conference, remission rate in our study patients was 66.7%. Level of GH dropped from median 19.50ug/l (range: 1.34-438.00ug/l) preoperative to median 1.52 ug/l (range 0.04-6.23ug/l) at first follow up (see figure 03). Level of IGF-1 dropped from median 801ug/l (range: 140-1349ug/l) to median 282 (range: 19-835ug/l). The other examined hormones remained around their preoperative levels. Median level of cortisol was 376nmol/l (range: 70-979nmol/l) at baseline and median 363nmol/l (range: 96-208nmol/l) after surgery, median TSH 1.63mU/l (range: 0.14-4.71mU/l) preoperative and median 1.59mU/l (range: 0.02-6.12mU/l) postoperative and prolactin median 13.50ug/l (range: 3.00-52.30ug/l) before surgery and median 9.00ug/l (range: 2.30-227.00ug/l) after surgery. Median fT4 was 15.40pmol/l (range: 9.90-20.30pmol/l) before and 16.90pmol/l (range: 11.90-22.00) after

surgery. There was no patient in need of cortisol or TSH substitution postoperative who has not been on replacement therapy before.

Regarding gonadal function, the median testosterone level in male patients was 8.80nmol/l (range: 3.30-19.40nmol/l) before and 12.30nmol/l (range: 2.60-20.60nmol/l) after surgery. Three male patients were on testosterone replacement therapy at evaluation for surgery and remained gonadotropin-deficient postoperatively. Eight female patients were postmenopausal at the time of surgery; in all of them, gonadotropin levels remained high following surgery. There was one female patient with insufficient menstrual function, and she also required estrogen replacement therapy following surgery.

In patients operated for the first time a remission rate of 73.5% was achieved whereas in patients with previous surgery a 20% remission rate was found. Patients referred for primary surgery had higher mean baseline levels of GH 54.18ug/l (range 1.44-438.00ug/l) vs 26.42ug/l (range 1.34-107.00ug/l) and larger tumor volume (7181mm^3 (range 132-56549mm^3) vs 1449mm^3 (range 50-4576mm^3) than patients subsequently being in remission. Furthermore, seven patients not being in remission (53.8%) but only three patientsin remission (11.5%) showed tumor invasion of the cavernous sinus. There were no differences in general patients' data, clinical symptoms and IGF-1 levels preoperative between the patients being in remission and those not being in remission.

Regarding the Hardy Classification[18] there were 11 patients of stage A, 11 patients of stage B, 12 patients of stage C, 3 patients of stage D and 2 patients of stage E. Remission rates were 72.3% for stage A and 72.3% for stage B patients, 75.0% for stage C patients, 0.0% for stage D patients and 50.0% for stage E patients.

Neuroradiological follow up:

At three months follow up there was no tumor remnant visible in diagnostic high-field MRI in 31 cases (79.5%). Of those 31 cases there were 26 which fulfilled the definition ofremission. In 5 patients there was no residual tumor detectable in high field diagnostic MRI but those patients still showed elevated GH levels and clinical symptoms of acromegaly. There were 8 patients with detectable residual tumor in diagnostic follow up MRI; one of those residual tumors was detected with iMRI, in a patient where tumor was left intentionally because of impossibility of complete tumor removal due to large tumor size (54*50*40mm^3), infiltration of cavernous sinus, caging of internal carotid artery and anterior cerebral artery and extensive into the hypothalamic region. Median residual tumor volume of those patients was 4mm^3 (range 4-168mm^3) in patients 5 patients after first time surgery and 52mm^3 (range 52-4691mm^3) for 3 patients with multiple previous surgery. Interestingly diagnostic high field MRI did not show residual tumor in 5 out of 13 patients not being in remission.

Discussion:

This study shows for the first time a series of 39 consecutive cases receiving transsphenoidal iMRI guided surgery for GH-producing PA applying an ultra-low-field iMRI (PoleStar™ N20). Our results show an overallremission rate of 66.7%. In patients without previous surgery theremission rate was even higher, 73.5%, and in previously operated patients theremission rate dropped to 20%. These results are at least as good as previously published series in literature showing a range of overallremission rates between 42% and 82%[1,2,5,6,7,11,13,15,17,19,21,25,29,30,33,34,35] .However in these publications the applied definition of remission differs widely (GH <1.0ug/l and <5.0ug/l). Definition of remission in this study was applied according to the international consensus conference. Studies with comparable definition of remission showed remission rates ranging from 52% to 67%[5,25,29].

Operations in patients with previous pituitary surgery showed a lower rate of remission (20.0%) than operations in patients with primary surgery. Such findings are in accordance with the literature showing remission rates between 20% and 30%[13,14,24,29].

Among the patients not being in remission there were an additional five patients (12.8%) with improvement or remission of clinical symptoms and reduction of GH excess to levels below 2.0ug/l. Although these patients were not defined as being in remission.

There have been few previous publications using intraoperative MRI for tumor resection control in pituitary surgery for acromegaly[4,14,16,32]. Fahlbusch et al published a series of patients operated with assistance of an intraoperative 1.5 Tesla iMRI and reported remission in 10 out of 23 patients (44%). Although the results of our study appears to compare well with those reported in the study by Fahlbusch et al., patients characteristics in the two small groups may not be fully comparable and considerably influence the surgical outcome; therefore, any claim for superiority between the two studies would be premature. In a study by Gerlach et al only part of the analyzed patients had GH positive adenomas[16]. Complication rate and neuroradiological tumor remnants were comparably low but endocrinological assessment was not performed.

Intraoperative imaging studies acquired with ultra low-field MRI scanner PoleStar N20 gave valuable and accurate information regarding tumor remnant after tumor removal. Only in two cases there was false negative interpretation regarding tumor remnant after first iMRI for resection control. Detection of tumor remnant led to an increase of 5.1% in remission rate as there were two patients being in remission where residual tumor was found on iMRI that could be completely resected. Despite this 5.1% increase of the remission rate we could only identify residual tumor with iMRI in 1 out of 8 patients with tumor residual in the diagnostic follow up MRI. Interestingly, the diagnostic high-field MRI was unable to visualize tumor residuals in 5 out of 13 patients that were endocrinologically

not being in remission. This indicates that even under optimal conditions, as in a diagnostic MRI environment, in five (12.8%) of 39 patients in the whole study group visualization of residual tumor could not be achieved, pointing to a systematic limitation of MRI for resection control.

Although the iMRI system was felt to be useful and led to improved remission rates the following limitations have to be considered. As in cases with additional tumor removal after iMRI scan following resection of the adenoma, there was a higher rate of false negative interpretation regarding tumor remnant. In these 7 of 8 cases with small adenoma residuals on postoperative diagnostic MRI a high rate (50%) of cavernous sinus tumor infiltration was present. This illustrates the limited visualisation of tumor remnants in the cavernous sinus as mentioned by previous studies[24]. As remission rates in patients with recurring disease were only 20%, it has to be stated, that iMRI in this difficult population was not as supportive as in patients with first time pituitary surgery. This may partially be caused by the insufficient differentiation of scar and recurrent adenoma tissue. High-field iMRI systems and imaging sequences with higher resolution of details may lead to a better definition of these structures; however an improved patients' outcome using high-field iMRI has not yet been demonstrated. Whether the costs related with iMRI systems used in pituitary surgery are compensated by improved outcome has to be shown by future investigations.

The surgical procedures described were safe. There was only one patient who developed signs of persisting CSF rhinorrhea and needed lumbar drainage for five days. Comparison with previous published studies showed rates of severe complications in up to 8% of cases and CSF rhinorrhea in around 2% of the cases[1,14,29]. One patient developed transient diabetes insipidus and needed temporary treatment with desmopressin. This

type of surgery appears to be quite safe for the remaining healthy pituitary cells; in fact, patients did not develop pituitary failure (even gonadotropin and sex hormone deficiency was rare) as confirmed in the follow up of these patients. Overall, complication rate was low and there were no severe complications such as postoperative hemorrhages, meningitis or injury to cranial nerves.

As all patients with PA in our department were operated in the iMRI since the year 2000 a comparison with patients operated without iMRI was not found to be adequate and is a limitation of this study.

Conclusions:

In this so far largest study for GH- producing PAs analyzing iMRI-guided transsphenoidal surgery the presented results suggest that this method is a highly effective and safe treatment modality, even compared to previously published surgical series using high-field iMRI. The overall remission rate of 66.7% and even 73.5% for patients without previous surgery and the lack of complications requiring additional surgery underscore this statement. Limitations of iMRI are the detection of small residuals in the cavernous sinus and persisting disease that could not be referred to even on diagnostic high-field follow-up MRIs. Further on analysis points to a systematic limitation of iMRI with regard to remission rates beyond 80% as even high field MRI under ideal conditions could not detect tumor residuals in 13% of cases. Detection of tumor remnant with iMRI and additional tumor removal led to a 5.1% increase of the remission rate.

Legends of tables and figures:

Table 01: Study and patients characteristics

Table 02: Pre-/postoperative median hormone levels

Table 03: Results of surgical procedures/Follow up

Table 04: Data of patients with first time surgery vs. patients with previous surgery

Table 05: Patient parameters with potential influence on duration of surgical procedures

Table 06: Patient overview

pt nr: patient number; ps: previous surgery; ds: duration of operation; hd: days of hospitalization; tv: tumor volume; ar: additional tumor removal after first intraoperative MRI for resection control; rs: tumor remnant at end of surgery; rf: tumor remnant at follow up; rz: size of tumor remnant at follow up; GH and IGF-1 level pre-/postoperative in ug/l; Values in brackets are results of glucose tolerance test, other values are base line results; y: yes; n: no

Figure 01: Flow chart of residual tumor detection in diagnostic high field MRI and iMRI

Figure 02: Pre-/intra- and postoperative imaging illustrative case
A: Preoperative 1,5 Tesla MRI, coronal view
B: Postoperative 1,5 Tesla MRI, coronal view
C: iMRI, coronal view, PoleStar N20 – before skin incision
D: iMRI, coronal view, PoleStar N20 – resection control after tumor removal, showing residual tumor
E: iMRI, coronal view, PoleStar N20 - iMRI after at the end of the surgical procedure showing no tumor residual

Figure 03: GH before and after surgery [ug/l] for 37 patients, log scale

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Table 01: Study and patients characteristics

Number of operations	39
Median patient age in years	46 [19-76]
Sex distribution, male	24 (61.5%)
Patients with previous pituitary surgery	5 (12.8%)
Preoperative tumor size ($mm^{3)}$	1319 [50-56549]
Infiltration of cavernous sinus	10
Patients with microadenoma	10 (25.6%)
Patients with macroadenoma	27 (69.2%)
Patients with giantadenoma	2 (5.1%)
Patients with symptoms of acromegaly	37 (94.8%)
Patients with cranial nerve palsy	12 (30.8%)

Table 02: Pre-/postoperative median hormone levels

	preoperative	postoperative
Growthhormone (GH) ug/l	19.50 [1.34-438.00]	1.52 [0.04-6.23]
Insulin like growth factor (IGF-1) ug/l	801 [140-1349]	282 [19-835]
Cortisol mmol/l	376 [70-979]	363 [96-808]
Thyroid stimulating hormone (TSH) uU/l	1.63 [0.14-4.71]	1.59 [0.02-6.12]
Thyroxine (T4) pmol/l	15.40 [9.90-20.30]	16.90 [11.90-22.00]
Testosterone nmol/l	8.80 [3.30-19.40]	12.30 [2.60-20.60]
Prolactine ug/l	13.50 [3.00-52.30]	9.00 [2.30-227.00]

Table 03: Results of surgical procedures/Follow up

Median intraoperative MRI studies per patient	2 [1-4]
Additional tumor removal after iMRI study for resection control	8 (20.5%)
Visible tumor remnant at end of surgical procedure	1 (2.6%)
Median duration of surgical procedure, minutes	90 [30-235]
Tumor remnant at three month follow up	8 (20.5%)
Mean time of overall follow up, month	29 [9-56]
Days of hospitalization	7 [5-17]
Patients with normalized hormone levels	30 (76.9%)
Patients in remission	26 (66.7%)

Table 04: Data of patients with first time surgery vs. patients with previous surgery

	first time surgery	with previous surgery
Number of patients	34	5
Median preoperative tumor volume (mm^3)	1572 [50-13722]	308 [168-56549]
Patients with intraoperative remnant removal	6 (17.6%)	2 (40%)
Patients without residual tumor at follow up	29 (85.3%)	2 (40%)
Patients with tumor remnant at follow up	5 (14.7%)	3 (60%)
Mean size of tumor remnant (mm^3)	4 [4-168]	52 [52-4691]
Patients with intra-/postoperative complications	0 (0.0%)	1 (20%)
Patients in remission	25 (73.5%)	1 (20.0%)

Table 05: Patient parameters with potential influence on duration of surgical procedures

Patient group	Duration of surgical procedere
Patients with first time surgery / with previous surgery	88 [30-180] / 105 [60-235]
Patients cured / not being in remission	72.5 [40-180] / 105 [30-235]
Patients with / without infiltration of cavernous sinus	118 [55-235] / 72.5 [30-170]

Table 06: Patient overview

pt nr	sex	age	ps	ds min	hd	tv (mm^3)	hc	ar	rs	rf	rz (mm^3)	GH preop.	IGF-1 preop.	GH postop.	IGF-1 postop.	In remission
1	M	46	y,1	105	6	506	B	n	n	y	220	1.44	281	6.13	371	n
2	M	29	n	180	7	268	E	n	n	n	-	31.20	996	[0.12]	328	y
3	M	70	n	116	6	785	B	n	n	n	-	14.00	544	3.30	19	n
4	F	66	n	90	7	523	A	n	n	n	-	7.97	776	-	350	y
5	M	64	n	60	8	829	B	n	n	n	-	31.20	709	[1.00]	152	y
6	M	42	n	125	6	1993	C	y	n	y	4	88.20	779	5.06	213	n
7	M	39	n	115	7	2278	C	n	n	n	-	25.40	859	[0.45]	330	y
8	M	52	n	95	8	1334	B	n	n	n	-	10.60	765	0.48	175	y
9	M	32	n	120	6	3364	C	n	n	n	-	107.00	1308	0.42	193	y
10	M	64	n	50	6	91	A	n	n	n	-	6.21	472	0.26	142	y
11	F	43	n	60	12	226	A	n	n	n	-	12.80	564	1.64	179	n
12	F	44	n	75	8	1238	B	n	n	n	-	20.30	461	0.48	218	y
13	M	66	n	170	9	1851	C	n	n	n	-	24.90	848	[<1.00]	304	y
14	F	51	n	95	7	2948	C	y	n	n	-	49.00	1007	[0.66]	431	y
15	M	37	n	95	5	4158	C	n	n	y	168	28.40	1307	3.09	405	n
16	M	38	y,1	60	7	167	A	n	n	n	-	1.34	245	0.82	181	y
17	F	38	n	40	8	1319	B	n	n	n	-	4.52	382	0.30	172	y
18	F	19	n	100	17	13722	D	y	n	y	147	438.00	900	6.84	835	n
19	F	20	y,1	140	7	307	B	y	n	y	52	15.90	702	4.39	735	n
20	M	32	n	85	8	4576	C	n	n	n	-	23.40	1085	0.51	251	y
21	M	49	n	105	8	5091	D	y	n	y	4	39.00	926	[1.51]	317	n
22	F	76	n	45	7	518	A	n	n	n	-	24.60	580	[0.08]	194	y
23	M	74	n	55	8	691	B	n	n	n	-	27.40	1020	2.00	206	y
24	F	53	n	100	7	2741	B	y	n	n	-	47.00	932	0.84	196	y
25	M	49	n	145	9	7225	E	y	n	y	4	12.30	801	6.23	376	n
26	M	58	n	75	7	131	A	n	n	n	-	23.00	140	1.38	409	n
27	M	45	n	140	9	50	A	n	n	n	-	5.09	801	0.42	394	y
28	M	54	n	50	6	424	A	n	n	n	-	6.85	553	0.42	278	y
29	F	44	n	30	7	2356	C	n	n	n	-	14.40	1158	1.05	351	n
30	M	28	n	55	5	1876	C	n	n	n	-	84.50	992	0.10	345	y
31	F	53	n	55	8	314	A	n	n	n	-	5.42	527	0.85	170	y
32	M	30	n	58	8	1238	B	n	n	n	-	47.90	1349	[<1.00]	603	y
33	F	64	n	50	8	226	A	n	n	n	-	4.13	403	0.85	151	y
34	F	45	y,2	60	10	301	A	n	n	n	-	1.53	447	1.40	439	n
35	M	30	n	70	6	1810	B	n	n	n	-	18.10	1053	0.14	260	y
36	F	53	n	115	7	3064	C	n	n	n	-	10.00	380	[0.39]	165	y
37	F	51	n	100	7	2089	C	n	n	n	-	19.50	1112	[0.52]	359	y
38	M	41	y,1	235	7	56548	D	y	y	y	4691	15.40	1081	3.90	480	n
39	M	48	n	60	6	1837	C	n	n	n	-	6.58	807	0.04	137	y

pt nr: patient number; ps: previous surgery; ds: duration of operation; hd: days of hospitalization; hc: Hardy classification; tv: tumor volume; ar: additional tumor removal after first intraoperative MRI for resection control; rs: tumor remnant at end of surgery; rf: tumor remnant at follow up; rz: size of tumor remnant at follow up; GH and IGF-1 level pre-/postoperative in ug/l; Values in brackets are results of glucose tolerance test, other values are base line results; y: yes; n: no

Fig 01

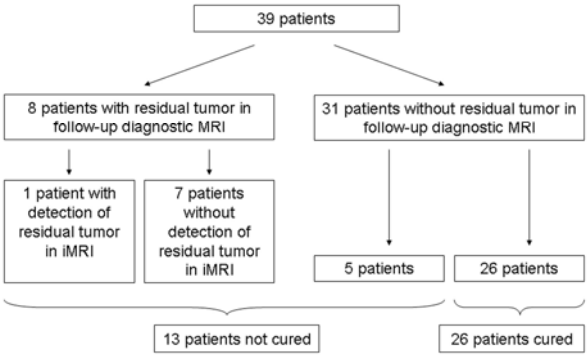

Fig 02D

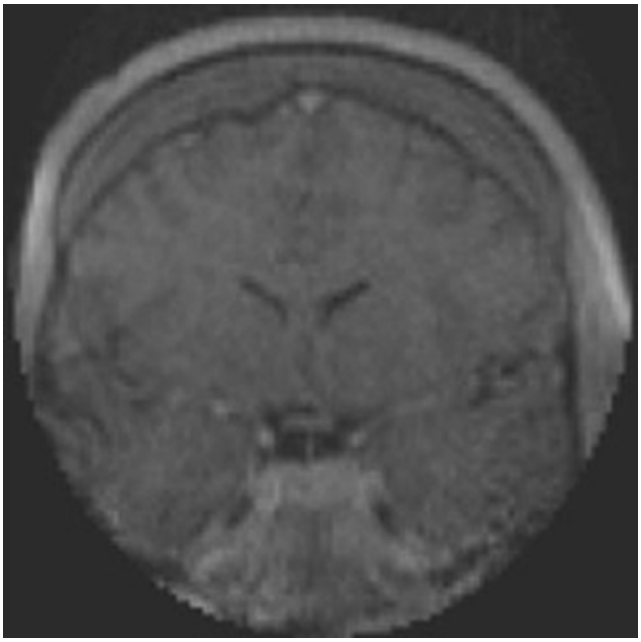

Fig 03

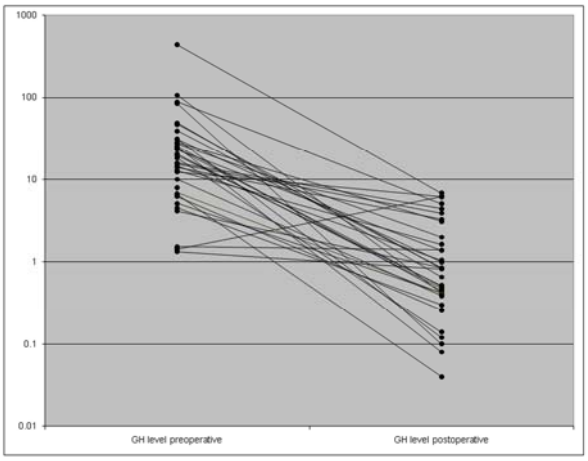

Fig 02A

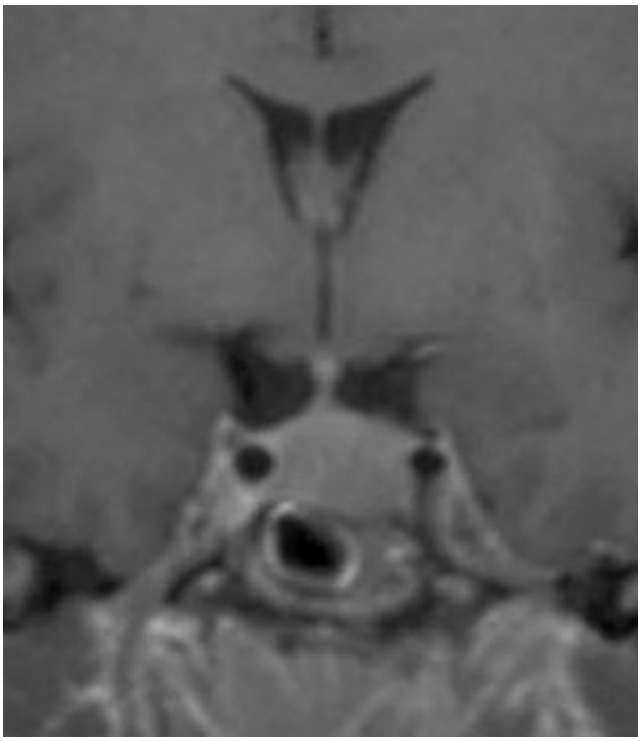

Fig 02E

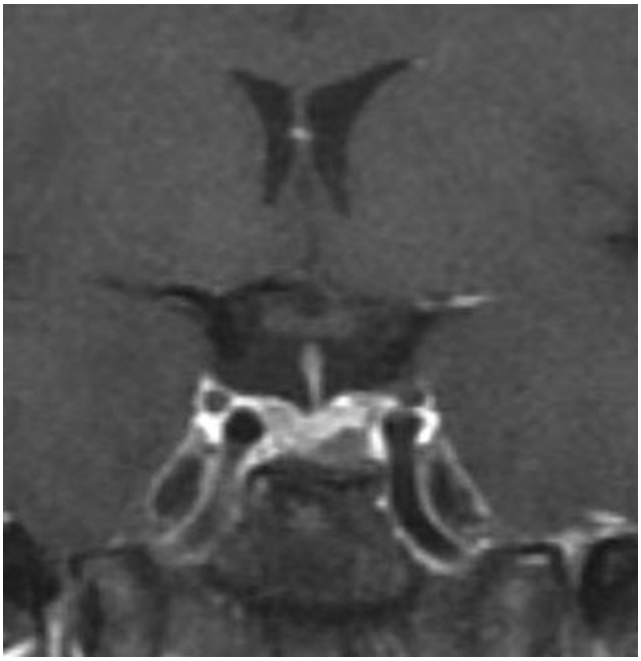

Fig 02C

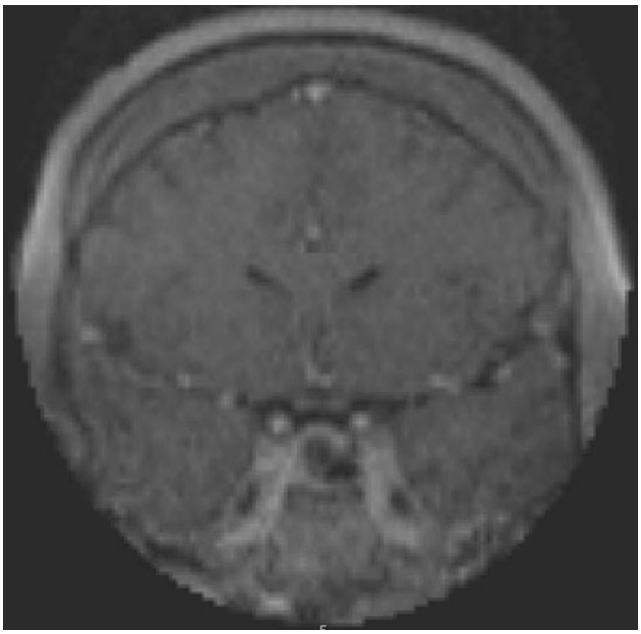

Fig 02B